

What is claimed is:

1. A protein binder which, when bound to human iRhom2, binds at least within a region of ~~Loop 1 thereof~~ human iRhom2 spanning from (and including) S474 to (and including) S660.
2. The protein binder of claim 1, which binds within at least a region of human iRhom2 spanning from (and including) W526 to (and including) I566.
3. The protein binder of claim 1 or 2, which binds a stretch of human iRhom2 comprising at least one residue selected from the group comprising W526; Q527; P532; P533; M534; D535; K536; S537; L539; K542; R543; T544; G546; R554; E557; S561; S562 and/or I566.
4. The protein binder according to any one of the aforementioned claims, which inhibits and/or reduces TACE/ADAM17 activity when bound to human iRhom2.
5. The protein binder according to any one of the aforementioned claims, wherein the inhibition or reduction of TACE/ADAM17 activity is caused by interference with iRhom2-mediated TACE/ADAM17 activation.
6. The protein binder according to any one of the aforementioned claims, which, when bound to human iRhom2,
 - inhibits or reduces induced TNF α shedding and/or
 - inhibits or reduces induced IL-6R shedding, and/or
 - inhibits or reduces induced HB-EGF shedding.
7. The protein binder according to any one of the aforementioned claims, wherein the human iRhom2 to which the protein binder binds comprises
 - a) the amino acid sequence set forth in SEQ ID NO 181, or
 - b) an amino acid sequence that has at least 80 % sequence identity with SEQ ID NO 181, with the proviso that said sequence maintains iRhom2 activity.

8. The protein binder according to any one of the aforementioned claims, which is a monoclonal antibody, or a target-binding fragment or derivative thereof retaining target binding capacities, ~~or an antibody mimetic~~, or

~~9. The protein binder according to any one of the aforementioned claims, which is an antibody in at least one of the formats selected from the group consisting of: IgG, scFv, Fab, or (Fab)₂.~~

~~109.~~ The protein binder according to any one of the aforementioned claims, which is not cross-reactive with human iRhom1.

~~110.~~ The protein binder according to any one of claims 8 - ~~109~~, which protein binder is an antibody that

a) comprises a set of heavy chain/light chain complementarity determining regions (CDR) comprised in the heavy chain/light variable domain sequence pair set forth in the following pairs of SEQ ID NOs:

2 and 7; 12 and 17; 22 and 27; 32 and 37; 42 and 47; 52 and 57; 62 and 67; 72 and 77; 82 and 87; 112 and 117; 152 and 157; 162 and 167; and/or 172 and 177;

b) comprises a set of heavy chain/light chain complementarity determining regions (CDR) comprising the following SEQ ID NOs, in the order (HCDR1; HCDR2; HCDR3; LCDR1; LCDR2 and LCDR3)

- 3, 4, 5, 8, 9, 10;
- 13, 14, 15, 18, 19, 20;
- 23, 24, 25, 28, 29, 30;
- 33, 34, 35, 38, 39, 40;
- 43, 44, 45, 48, 49, 50;
- 53, 54, 55, 58, 59, 60;
- 63, 64, 65, 68, 69, 70;
- 73, 74, 75, 78, 79, 80;

- 83, 84, 85, 88, 89, 90;
- 113, 114, 115, 118, 119, 120;
- 153, 154, 155, 158, 159, 160;
- 163, 164, 165, 168, 169, 170; and/or
- 173, 174, 175, 178, 179, 180;

c) comprises the heavy chain/light chain complementarity determining regions (CDR) of b), with the proviso that at least one of the CDRs has up to 3 amino acid substitutions relative to the respective SEQ ID NOs, and/or

d) comprises the heavy chain/light chain complementarity determining regions (CDR) of b) or c), with the proviso that at least one of the CDRs has a sequence identity of $\geq 66\%$ to the respective SEQ ID NOs,

wherein the CDRs are embedded in a suitable protein framework so as to be capable to bind to human iRhom2 with sufficient binding affinity and to inhibit or reduce TACE/ADAM17 activity.

~~42~~11. The protein binder according to any one of claims 8 - ~~44~~10, which comprises

a) the heavy chain/light chain variable domain (HCVD/LCVD) pairs set forth in the following pairs of SEQ ID NOs:

2 and 7; 12 and 17; 22 and 27; 32 and 37; 42 and 47; 52 and 57; 62 and 67; 72 and 77; 82 and 87; 112 and 117; 152 and 157; 162 and 167; and/or 172 and 177;

b) the heavy chain/light chain variable domains (HCVD/LCVD) pairs of a), with the proviso that

- the HCVD has a sequence identity of $\geq 80\%$ to the respective SEQ ID NO, and/or
- the LCVD has a sequence identity of $\geq 80\%$ to the respective SEQ ID NO,

c) the heavy chain/light chain variable domains (VD) pairs of a) or b), with the proviso that at least one of the HCVD or LCVD has up to 10 amino acid substitutions relative to the respective SEQ ID NO,

said protein binder still being capable to bind to human iRhom2 with sufficient binding affinity and to inhibit or reduce TACE/ADAM17 activity.

~~13~~12. The protein binder according to any one of claims 8 – ~~12~~11, wherein at least one amino acid substitution is a conservative amino acid substitution.

~~14~~13. The protein binder according to any one of the aforementioned claims, which protein binder has at least one of

- target binding affinity of $\geq 50\%$ to human iRhom2 compared to that of the protein binder according to any one of the aforementioned claims, and/or
- $\geq 50\%$ of the inhibiting or reducing effect on TACE/ADAM17 activity of the protein binder according to any one of the aforementioned claims.

~~15.~~ A protein binder that binds to human iRhom2, and competes for binding to human iRhom2 with

a) ~~an antibody according to any one of claims 8 – 14, or~~

b) ~~an antibody selected from the group consisting of clones #3, #5, #16, #22, #34, #42, #43, #44, #46, #49, #54, #56, or #57~~

~~16.~~ A protein binder that binds to essentially the same, or the same, region on human iRhom2 as

a) ~~an antibody according to any one of claims 8 – 14, or~~

b) ~~an antibody selected from the group consisting of clones #3, #5, #16, #22, #34, #42, #43, #44, #46, #49, #54, #56, or #57.~~

~~17~~14. A nucleic acid that encodes for at least one chain of the binding agent according to any one of the aforementioned claims.

~~48~~15. Use of the protein binder according to any one of claims 1 – ~~46~~13 (for the manufacture of a medicament) in the treatment of a human or animal subject

- being diagnosed for,
- suffering from or
- being at risk of developing

an inflammatory condition, or for the prevention of such condition.

~~49~~16. A pharmaceutical composition comprising the protein binder according to any one of claims 1 – ~~46~~13 or the nucleic acid according to claim ~~47~~14, and optionally one or more pharmaceutically acceptable excipients.

~~20~~17. A combination comprising (i) the protein binder according to any one of claims 1 – ~~46~~13, the nucleic acid according to claim ~~47~~14, or the pharmaceutical composition according to claim ~~49~~16 and (ii) one or more therapeutically active compounds.

~~21~~18. A method for treating or preventing an inflammatory condition, which method comprises administration, to a human or animal subject, of (i) the protein binder according to any one of claims 1 – ~~46~~13, (ii) the nucleic acid according to claim ~~47~~14 (iii) the pharmaceutical composition according to claim ~~49~~16 or (iii) the combination according to claim ~~20~~17, in a therapeutically sufficient dose.

~~22~~19. The use of claim ~~48~~15 or the method of claim ~~21~~18, wherein the inflammatory condition is Rheumatoid Arthritis (RA)

~~23~~20. A therapeutic kit of parts comprising:

- a) the protein binder according to any one of claims 1 – ~~46~~13, the nucleic acid according to claim ~~47~~14, the pharmaceutical composition according to claim ~~49~~16 or the combination according to claim ~~20~~17,
- b) an apparatus for administering the composition, composition or combination, and
- c) instructions for use.